

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BPG-33314ABCK	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/EP2004/009067	International filing date (day/month/year) 12.08.2004	Priority date (day/month/year) 13.08.2003	
International Patent Classification (IPC) or national classification and IPC C12N15/63, C12N15/21, C07K14/56			
Applicant SANDOZ AG et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> <i>(sent to the applicant and to the International Bureau)</i> a total of sheets, as follows:</p> <ul style="list-style-type: none"> <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only)</i> a total of (indicate type and number of electronic carrier(s)), containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application 			
Date of submission of the demand 24.05.2005	Date of completion of this report 01.08.2005		
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epru d Fax: +49 89 2399 - 4465	Authorized Officer BULCAO DE MELO BARRE Telephone No. +49 89 2399- 8972		



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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - international search (under Rules 12.3 and 23.1(b))
 - publication of the international application (under Rule 12.4)
 - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-31 as originally filed

Sequence listings part of the description, Pages

1-11 received on 29.10.2004 with letter of 27.10.2004

Claims, Numbers

1-41 as originally filed

a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

- The amendments have resulted in the cancellation of:
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):
- This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-41
	No: Claims	
Inventive step (IS)	Yes: Claims	1-41
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-41
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 in written format
 in computer readable form
 - c. time of filing/furnishing:
 contained in the international application as filed
 filed together with the international application in computer readable form
 furnished subsequently to this Authority for the purposes of search and/or examination
 received by this Authority as an amendment on
2. In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional observations, if necessary:

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1. Reference is made to the following documents:

D1: Biochimie, Vol. 72, 1990, pages 407-415

D2: Journal of Bacteriology, Vol. 163, No. 3, 1985, pages 1222-1228

SECTION V

2 **Novelty (Article 33(2) PCT)**

The subject-matter of the present application does not appear to be disclosed in the prior art as defined in the regulations (**Rule 64 (1)-(3) PCT**).

Therefore, in view of such prior art the subject-matter of the present application (**claims 1-41**) has to be regarded as being new (**Article 33(2) PCT**).

3 **Inventive Step (Article 33(3) PCT)**

The **closest prior art** to evaluate the inventiveness of the present application (**claims 1-41**) is document **D1**, which discloses the periplasmic expression of an heterologous protein (ferredoxin) in a prokaryotic microorganism (*Escherichia coli*). The periplasmic expression is achieved by the use of an expression vector which contains the OmpA signal peptide.

Starting from **D1**, the underlying **technical problem** to be solved by the present application can be considered to lie in the provision of an alternative way to direct the expression of heterologous proteins into the periplasm of the host cell.

The **solution** provided by the Applicant to solve the above problem lies in the use of an expression vector which comprises the signal peptide of the *gac* (glutaryl 7-aminocephalosporanic acid acylase) gene of *Pseudomonas diminuta*.

Document **D2** discloses the molecular cloning and structure of the gene for glutaryl 7-aminocephalosporanic acid acylase from a *Pseudomonas* strain. Although **D2** suggest that this enzyme appears to be periplasmic in *Pseudomonas*, it does not provide any clear indication that this is indeed the case nor any experiments that

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would prove that the acylase activity is found in the periplasm in *E. coli*.

There is no indication in the prior art that would teach the person skilled in the art to select the signal peptide of the *gac* gene among the large number of periplasmic genes known in the art. In particular, in view of D2, which does not provide a reasonable expectation of success, the person skilled in the art would not consider the signal peptide of the *gac* gene to secrete foreign proteins into the periplasm. None of the available prior art documents, including D2, suggests the use of the signal peptide of the *gac* gene to direct the expression of a heterologous protein into the periplasm of the host cell.

The *gac* expression system of the present invention is particularly suitable for use in a process for the efficient and direct production of mature recombinant proteins of interest in pure form in a high yield.

Therefore, the subject-matter of the present application (**claims 1-41**) is considered to involve an inventive step (**Article 33(2) PCT**).

SECTION VIII

4. Clarity (Article 6 PCT)

Claim 13 is directed to a vector but it depends on claim 10, which is directed to a host cell. This renders claim 13 unclear. It appears that claim 13 should rather be drafted as "the host cell according to claim 10".

The same objection applies to **claim 14**.